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PART III

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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NITRATES AND NITRITES IN POULTRY PRODUCTS

Statement of Policy; Request for Data

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 77N-0222]

NITRATES AND NITRITES IN POULTRY PRODUCTS

Statement of Policy; Request for Data

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs determines that nitrates and nitrites as currently used in manufacturing poultry products are food additives, and he establishes a program for obtaining information required to resolve definitively questions about their safe use. The agency will entertain requests for the issuance of interim food additive regulations authorizing the continued use of nitrates and nitrites in poultry products, if the requests are accompanied by a commitment to conduct testing to demonstrate (1) that the requested uses do not result in the formation of cancer-causing nitrosamines before the food is ingested; (2) that the requested levels of nitrates or nitrites are otherwise safe for human consumption; and (3) that use as a preservative is necessary to prevent the growth of *Clostridium botulinum* and the resulting production of botulinal toxin in the food.

DATE: Written requests for issuance of interim food additive regulations and comments from interested persons must be submitted on or before November 1, 1977.

ADDRESS: Written requests, supporting data and information, and other comments should be submitted (in quadruplicate) to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

John J. McAuliffe, Bureau of Foods (HFF-334), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, D.C. 20204 (202-472-5690).

SUPPLEMENTARY INFORMATION: This document sets forth and explains the conclusion of the Commissioner of Food and Drugs that nitrates (sodium nitrate ($NaNO_3$), also known as soda niter, nitrate of soda and chile saltpeter; and potassium nitrate (KNO_3), also known as saltpeter and nitrate of potash) and nitrites (sodium nitrite ($NaNO_2$); potassium nitrite (KNO_2)), if used as preservatives or characterizing ingredients in the manufacture of poultry products, such as smoked poultry, chicken hot dogs, and turkey hams, are considered food additives under section 201(s) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(s)). The same substances may be color additives under section 201(t) of the act (21 U.S.C. 321(t)), if used essentially for the purpose of affecting color. This notice outlines the conditions under which such substances may continue to be used in poultry products, and establishes a schedule for resolving persistent issues concerning the safety of these substance.

Pursuant to § 180.1 (21 CFR 180.1), the Commissioner will entertain requests for the issuance of interim food additive regulations authorizing the use of nitrates and nitrites in poultry products, pending the conduct of prescribed safety tests. Further, the Commissioner will, in response to proper request, consider the inclusion of nitrates and nitrites on the list of provisionally approved color additives, subject to the conditions specified below. Such requests must be submitted to the Food and Drug Administration (FDA) within 60 days, accompanied by specified information and by commitments to undertake, and report to the agency the results of, three types of safety-related tests. Food or color additive petitions in the format set forth in § 71.1 or § 171.1 (21 CFR 71.1 or 171.1) will also be necessary if these substances are to be considered for long-term approval as food or color additives.

The Commissioner also invites the submission of data and views from any interested person respecting the use of nitrates and nitrites in poultry products, including (1) the need for, and appropriateness of, continued use of nitrates and nitrites in specific types of poultry products, (2) the safety of nitrates and nitrites, and (3) the potential for nitrates or nitrites to form nitrosamines in poultry products prior to their ingestion by humans. The Commissioner is particularly interested in receiving views bearing on the nature of any further long-term testing necessary to resolve conclusively issues about the safety of nitrates and nitrites as curing agents in poultry products.

Comments on this notice, and any pertinent information, should be submitted to the Hearing Clerk at the above address by November 1, 1977, to permit evaluation at the same time that the agency is considering any requests for interim food additive status or provisional color listing.

If the Commissioner receives requests for interim food additive status or provisional color listing supported by reasonable grounds, he will issue proposals to that effect in the FEDERAL REGISTER and invite submission of further comments before taking final action on the requests. Should the Commissioner determine that any requested use of nitrates or nitrites in poultry fails to provide reasonable grounds to support issuance of a proposal, he will deny the request and determine that the use is unlawful. The Commissioner will not permit the use of nitrites in any poultry product in which nitrosamines are found prior to ingestion by humans. However, pending submission of requests for interim food additive status and final action by FDA, current uses of nitrates and nitrites in poultry products will not be regarded by FDA as causing the products to be adulterated under the act.

BACKGROUND

Nitrates and nitrites have long been used in the curing of several types of poultry products, in some instances for at least 30 years. Previously, FDA has considered such uses to be covered by "prior sanctions" issued before September 6, 1958, by the U.S. Department of Agriculture (USDA) under the Poultry Products Inspection Act (21 U.S.C. 451 et seq.). Those uses were thus not subject to the food additive provisions of sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(s) and 348). On April 22, 1977, and on July 15, 1977, however, the Commissioner received letters from the Assistant Secretary of Agriculture for Food and Consumer Services, Ms. Carol Tucker Foreman, which conclude, based on available information, that USDA had not officially approved the use of nitrates and nitrites in poultry products under the Poultry Products Inspection Act before passage of the Food Additives Amendment of 1958 and that, therefore, such uses are not covered by valid prior sanctions. Assistant Secretary Foreman asked the Commissioner to determine whether use of nitrates and nitrites in poultry products is considered a food additive or color additive use and whether those uses are safe.

The clarification by USDA of its position on the prior sanction status of nitrates and nitrites in poultry products has prompted a reexamination of FDA's own understanding of the status of these compounds, resulting in the issuance of this notice. The Food and Drug Administration has no basis for independently questioning Ms. Foreman's conclusion, and further, the Commissioner believes that the conclusion of USDA about whether it had issued, for these uses, prior sanctions that satisfy the terms of section 201(s) of the act is dispositive.

Furthermore, as a matter of policy the Commissioner has for some time maintained that the category of prior-sanctioned substances used in food represents an anomaly in the law. This anomaly justifies a narrow construction of those provisions that shelter compounds used as food additives from the basic requirements of the Food Additives Amendment of 1958. Debate over the prior-sanctioned status of nitrates and nitrites has for too long deflected attention from the central issues on the use of these substances. These issues include (1) whether nitrates or nitrites are useful in reducing the risk of botulism that could result from the ingestion of contaminated poultry products, (2) whether nitrates or nitrites form cancer-causing nitrosamines in poultry products prior to ingestion, and (3) whether nitrates or nitrites are otherwise safe for human consumption. The Commissioner concludes, with Assistant Secretary Foreman, that the time has come to assemble the data required to resolve these questions.

History of the Use of Nitrates and Nitrites in Poultry Products

Nitrates and nitrites have been used for centuries, directly or indirectly, in the curing of meat and poultry. The unique organoleptic qualities of cured meats and some poultry products are often the result of the use of nitrates and nitrites. At the present time nitrates and nitrites are used in the production of such foods to preserve them and to impart the taste, texture, and color that consumers, through long exposure, have come to associate with such foods.

Nitrates (sodium nitrate ($NaNo_3$) and potassium nitrate (KNO_3)) and nitrites (sodium nitrite ($NaNO_2$) and potassium nitrite (KNO_2)) are water soluble inorganic salts. Nitrates are transformed to nitrites in food and in the gastrointestinal tract through bacterial and enzymatic action. It is possible, but as yet not well documented, that nitrates may also be transformed to nitrites in meat by strictly chemical reactions.

Appreciation of the role of nitrates and nitrites in retarding growth of and toxin development by *Clostridium botulinium* has increased over the last 40 years. *C. botulinum* is a microorganism that is ordinarily quite harmless when naturally present in the soil or in the sea. *C. botulinum* becomes a source of concern only when it grows in food; it then produces a toxin which, if ingested, causes botulism, an acute food poisoning marked by a high mortality rate. Nitrates and nitrites have been shown to be effective in inhibiting the growth of *C. botulinum* in chopped ham (Christiansen, L. N., et al., "Effect of Nitrite and Nitrate on Toxin Production by *Clostridium botulinum* and on Nitrosamine Formation in Perishable Canned Comminuted Cured Meat," Applied Microbiology, 25:357 (1973)); in bacon (Christiansen, L. N., et al., "Effect of Sodium Nitrite on Toxin Production by *Clostridium botulinum* in Bacon," Applied Microbiology, 27:733 (1974)); in wieners (Hustad, G. O., et al., "Effect of Sodium Nitrite and Sodium Nitrate on Botulinal Toxin Production and Nitrosamine Formation in Wieners," Applied Microbiology, 26:22 (1973)); in summer style sausage (Christiansen, L. N., et al., "Effect of Sodium Nitrite and Nitrate on *Clostridium botulinum*. Growth and Toxin Production in a Summer Style Sausage," Journal of Food Science, 40:488 (1975)); and in some smoked fish (unpublished data).

Several literature references document the long use of nitrates and nitrites in the curing of poultry products, and reflect the growth of commercial use of these substances. For example, in October 1938, A. K. Besley and S. J. Marsden of the USDA Bureau of Animal Industry, issued (A&D No. 28) "Suggestions for Curing and Smoking Turkeys," and stated: "A suitable curing mixture consists of 6 pounds of salt, 3 pounds of sugar and 2 ounces of saltpeter (potassium nitrate) dissolved in 4½ gallons of water. This pickle contains approximately 13 percent of salt and has a salinometer reading of about 70° at a temperature of 38° F. Experience has shown that about four times this indicated quantity of pickle is required to cover 100 pounds of moderately large, drawn turkeys when packed carefully in a 50-gallon barrel."

In 1941, P. J. Schaible and J. A. Davidson of the Chemistry and Poultry Sections, Michigan Agricultural Station, wrote in "Boning, Curing, and Smoking Poultry Meat," The U.S. Egg and Poultry Magazine, pp. 228–230, and 255–256: "In small numbers, poultry has been cured and smoked for many years on farms. Although the product has not been uniform in appearance or taste and has been high priced, customers have shown sufficient interest to encourage a few firms specializing in unusual meat delicacies to enter the field. Goose breasts and legs have been cured and smoked for some time, but of recent years attention has been directed to turkey." Saltpeter (potassium nitrate) is included in the curing formulations given. In 1941, Besley and Marsden of USDA, in "A Study of Turkey Curing and Smoking," Poultry Science, pp. 496–506, presented some of the experimental evidence obtained in studying the curing and smoking of turkeys. The authors stated: "The presence of saltpeter in the cure resulted in a pink cast to the white meat and a rich, red-colored dark meat, typical of cured lean pork."

In the past few years, many new food products have been developed using poultry in lieu of red meat. Sodium nitrite is used in many of these products, which have the same basic characteristics as red meat items and are known by such names as "Chicken Hot Dogs," "Chicken Franks," and "Turkey Ham." The use of chicken in hot dogs was sanctioned by USDA on October 3, 1969.

It is the responsibility of FDA to evaluate the safety of all additives to foods, including meat, poultry, and egg products, and to publish regulations prescribing safe conditions of use. However, USDA has responsibility for enforcing quantitative restrictions and assuring proper use of additives in meat, poultry, and egg products. Furthermore, USDA has independent authority to prohibit use of food additives in meat and poultry, even though their use may have been approved by FDA.

Safety of Nitrates and Nitrites in Poultry Products

Current USDA requirements specify that the use of nitrates, nitrites, or any combination of these, shall not result in more than 200 parts per million (ppm) nitrite, calculated as sodium nitrite, in the finished product (9 CFR 381.147(f)(3)). This apparently was the amount considered necessary to accomplish the desired characterizing and preservative effects.

Nitrates occur in practically all parts of the environment but primarily in water and vegetables. It has been estimated that the drinking water consumed by an average resident in the United States contains 0.7 ppm nitrate and that the average nitrate content of vegetables ranges from 13 ppm in dry beans to 2,760 ppm in beets (White, J. W., Jr., "Relative Significance of Dietary Sources of Nitrate and Nitrite," Journal of Agricultural and Food Chemistry, 23:886 (1975), as corrected in the same journal, 24:202 (1976)). Leafy vegetables such as lettuce, cabbage, and broccoli are also high in nitrates. Nitrates have a very low toxicity that has been reported to be of the same order as the toxicity of sodium chloride (Institute of Food Technologists' Expert Panel on Food Safety and Nutrition, "Nitrites, Nitrates, and Nitrosamines in Food—a Dilemma," Food Technology/Journal of Food Science, 37:989 (1972). Sodium nitrate has been fed to rats up to 10 percent in the diet for their lifetime. Other than some depression in growth at levels above 1 percent, no adverse effects were noted in these animals (Lehman, A. J., "Nitrates and Nitrites in Meat Products," Association of Food and Drug Officials, U.S. Quarterly Bulletin, 22:136 (1958)).

Nitrites, on the other hand, occur less frequently in the environment but are more toxic. In pigs that were fed up to 18.3 milligrams of potassium nitrite per kilogram of body weight there was no effect on weight gain or feed efficiency, but methemoglobinemia (impairment of ability of blood to carry oxygen) was apparent. When fed potassium nitrite at more than 21.3 mg/kg body weight, the pigs died (London, W. T., et al., "An Attempt to Produce Chronic Nitrite Toxicosis in Swine," Journal of the American Veterinary Medical Association, 150:398 (1967)). Methemoglobinemia is also seen in man, particularly in infants accidentially exposed to nitrites (Committee on Nutrition, "Infant Methemoglobinemia. The Role of Dietary Nitrate," Pediatrics, 46:475 (1970)).

Nitrites have not been shown to be carcinogenic or teratogenic at any dose level. However, additional research is currently being carried out. A recent report in Science, 196:1,000 (1977) discussed the mutagenic activity of nitrite-treated foods. Extracts of Japanese raw fish, beef, and hot dogs treated with nitrite were evaluated using the *Salmonella typhimurium* test. The raw fish extracts exhibited mutagenic activity, but the beef and hot dog samples were not mutagenic. Additionally, FDA has supported a dominant lethal study in rats on potassium nitrite and potassium nitrate. These studies, funded under contract to Stanford Research Institute, were recently completed (June 1977). Preliminary conclusions indicate that potassium nitrate is nonmutagenic in the rat, and that potassium nitrite may be a mutagen in the rat at 112, 373, and 1,120 ppm in the diet.

R. Preussman has reviewed the chronic toxicity of nitrites (Proceedings of the International Symposium on Nitrite in Meat Products, held at the Central Institute for Nutrition and Food Research TNO, ZEIST, the Netherlands, September 10–14, 1973, pp. 217–226) and summarizes the work of several investigators. One investigator (Druckery) gave 100 milligrams of nitrite per kilogram of body weight to rats over the lifespan of

three generations. Except for a (probably not significant) shortening of the lifespan and a reduction in hemoglobin concentration, no adverse toxic effects of the treatment were noted; reproduction of treated animals was not affected and no teratogenic effects were observed in the offspring. Another investigator (Sander) added 1 percent sodium nitrite to the diet of rats for 117 days and observed the animals until natural death; he saw no tumors or other serious toxic effect.

An ongoing study with sodium nitrite in the rat is discussed later in this document in connection with a study involving the simultaneous feeding of sodium nitrite and an amine in rats.

Although the values for the ingestion of nitrates and nitrites by the population of the United States are not well documented, J. White ("Relative Significance of Dietary Sources of Nitrate and Nitrite," Journal of Agricultural and Food Chemistry, 23:886 (1975) as corrected in the same journal 24:202 (1976)) has estimated the average daily ingestion of nitrates and nitrites for a United States resident to be 99.8 and 11.22 milligrams, respectively. More than four-fifths of the dietary intake of nitrates is from vegetables and less than one-tenth from cured meats, including poultry products. Three-fourths of the nitrite entering the human stomach originates in saliva, and approximately one-fifth from cured meats including poultry products.

While nitrites have not been shown to be carcinogenic, it is known that nitrites can, under certain conditions, combine with secondary or tertiary amines to form compounds known as nitrosamines. There are many different nitrosamines, some of which are known carcinogens. Nitrosamines have been detected occasionally at low levels in various cured meat products, but not with any consistency in any except fried bacon. Nitrosamines were detected in 3 out of 34 frankfurter samples at 11 to 84 parts per billion (Wasserman, A. E., et al., "Dimethylnitrosamine in Frankfurters," Food and Cosmetics Toxicology, 10:681 (1972)), in 5 out of 59 prepared meat products at 10 to 80 parts per billion (Sen, N. P., "The Evidence of Presence of Dimethylnitrosamine in Meat Products," Food and Cosmetics Toxicology, 10:219 (1972)), and in 1 ham sample out of 51 samples of various meat products, at 5 parts per billion (Fazio, T., et al., "Analysis of Nitrite and/or Nitrate—Processed Meats for N–Nitrosodimethylamine," Journal of the Association of Official Analytical Chemists, 54:1157 (1971)). N–Nitrosopyrolidine was detected in all 22 samples of fried bacon at levels up to 139 parts per billion (Havery, D. C., et al., "Survey of Food Products for Volatile N–Nitrosamines," Journal of the Association of Official Analytical Chemists, 59:540 (1976)). Cured poultry products have not been comprehensively examined to determine whether they contain nitrosamines. Indications of traces of apparent nitrosamines were observed in two of four chicken frankfurter products recently examined in an FDA laboratory.

The mutagenic properties of nitrosamines have been studied extensively in various systems. McCann et al. document nitrosamine compounds which have been shown to be mutagenic in selected bacterial test systems (Proceedings of the National Academy of Sciences of the USA, 72:5135 (1975)).

Nitrosamines have been formed experimentally in the gastrointestinal tracts of mice, rats, and rabbits by simultaneous administration of nitrites and secondary amines. In vitro experiments have shown for both animals and man that nitrosamine formation can occur under conditions normally present in the stomach (Sen, N. P. et al., "Formation of *N*–Nitrosamines from Secondary Amines and Nitrite in Human and Animal Gastric Juice," Food and Cosmetics Toxicology, 7:301 (1969)). It is not known whether this phenomenon is increased or even affected by ingestion of foods containing nitrites. In human subjects with gastric hypoacidity (low stomach acidity) who were administered a drink containing both diphenylamine and sodium nitrate, bacterial reduction of nitrate to nitrite and formation of diphenylnitrosamine (a noncarcinogen) was demonstrated (Sander, J. and F. Seif, "Bacterial Reduction of Nitrate in the Human Stomach, as a Cause of Nitrosamine Formation," Arzneimittel Forschung, 19:1091 (1969)).

Cancer has occurred in laboratory animals in experiments in which high levels of nitrites and secondary amines were fed to the animals. These experiments indicate the possibility of the formation of carcinogenic nitrosamines in the bodies of animals. As would be expected, the levels of nitrites employed in these studies far exceeded the levels commercially used in human foods. A study conducted recently at the Massachusetts Institute of Technology under FDA contract (R. C. Shank and P. M. Newberne, "Dose-Response Study of the Carcinogenicity of Dietary Sodium Nitrite and Morpholine in Rats and Hamsters," Food and Cosmetics Toxicology, 14:1 (1976)), although possibly flawed, has suggested a dose-response relationship for the induction of liver and lung tumors in rats fed combinations of sodium nitrite and morpholine (a cyclic amine) when the nitrite levels in the diet were of the order used in commercially prepared human foods.

The study also suggests, in the rat, a possible relationship between the feeding of sodium nitrite alone and an increased incidence of lymphoreticular tumors. The significance of these tumors is, however, unclear because of a variety of uncertainties with respect to the feeding of nitrite alone in this study. These uncertainties include the possible interaction of nitrite with the semisynthetic diet that was used, the possible influence of the diet itself, and the fact that in this study, as in other studies of combined nitrite and secondary amine, the nitrite group itself represented a control group. Because of these uncertainties, FDA has sponsored an additional study to examine directly the questions of potential nitrite carcinogenicity. This study is nearing completion and to date has shown no indication that sodium nitrite is carcinogenic.

Questions about the potential carcinogenicity of nitrites have persisted for several years, and have dominated discussions about the proper regulatory action on their continued use. In 1973, the Secretary of Agriculture established an Expert Panel on Nitrites, Nitrates, and Nitrosamines, consisting of scientific experts both within and outside government, to advise him whether the use of nitrates and nitrites in the curing of meats and poultry constituted a public health hazard, and if so, whether such use should be restricted or prohibited.

The USDA Expert Panel is to conclude its deliberations in September 1977 and to thereafter make recommendations to the Secretary of USDA. The recommendations will address such considerations as the levels of nitrite in all cured meat products; the formation of nitrosamines and an evaluation of their dangers; evaluation of currently available alternatives to nitrite use; and a review of products, if any, in which nitrites are used solely for color or other organoleptic purposes.

Legal Status of Nitrates and Nitrites in Poultry Products

Section 201(s) of the Federal Food, Drug, and Cosmetic Act defines "food additive" as follows:

The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food * * * if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—

* * * * *

(3) A color additive; or

(4) Any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following) * * *.

Under this definition, substances sanctioned by USDA for use in poultry products under the Poultry Products Inspection Act prior to the enactment of the Food Additives Amendment of 1958 (September 6, 1958) are not considered "food additives". A substance that is prior-sanctioned need not be covered by an effective food additive regulation in order to be used, nor need its safety have been demonstrated in accordance with

modern toxicological standards. If FDA determines that such a substance is not safe, the agency has the burden of demonstrating that it causes foods in which it is used to be adulterated under section 402(a)(1) or (2)(A) of the act (21 U.S.C. 342(a)(1), (2)(A)). Furthermore, because they are not food additives, prior-sanctioned substances are not subject to section 409(c)(3)(A) (the Delaney anticancer clause) of the act (21 U.S.C. 348(c)(3)(A)).

Section 201(t)(1) of the act defines "color additive":

The term "color additive" means a material which—

(A) Is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source and

(B) When added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used or intended to be used) solely for a purpose or purposes other than coloring.

This definition makes no provision for continued use of substances that had been sanctioned by FDA or USDA prior to enactment of the Color Additive Amendments of 1960. However, the amendments permited the "provisional listing" and continued use, pending completion of safety testing, of substances meeting the definition of a color additive already in use in food in 1960.

There are no FDA regulations that independently authorize the commercial use of nitrates and nitrites in poultry products, either as food additives or as color additives, nor has FDA itself issued a prior sanction permitting their use. In § 170.60(b) (21 CFR 170.60(b)), FDA regulations do, however, recognize their use, based on the belief that USDA had issued valid prior sanctions.

The longstanding use of nitrates and nitrites in poultry products is reflected in several documents. Ms. Foreman's letter indicates that, as far back as November 20, 1958, USDA authorized the use of nitrates and nitrites for specific purposes in certain poultry products. Additionally, USDA issued the Products Inspection Regulations, published in the FEDERAL REGISTER of May 16, 1972 (37 FR 9706), which include nitrates and nitrites on the list of substances permitted to be used in poultry. Nitrates and nitrites appear under the heading, "Curing agents," for the listed purpose "to fix color" (9 CFR 381.147(f)(3)).

FDA's belief that § 381.147(f)(3) rested on a prior USDA sanction is reflected in FDA's own proposal on nitrates and nitrites published in the FEDERAL REGISTER of November 3, 1972 (37 FR 23456). A portion of that proposal (proposed §§ 121.2007 and 121.2008 (21 CFR 121.2007 and 121.2008)) would have established regulations recognizing and governing the prior-sanctioned uses of nitrates and nitrites in both meat and poultry products. Proposed §§ 121.2007 and 121.2008 would have listed amounts of nitrates and nitrites for use in poultry, as well as meat products, that coincide with the levels specified in § 381.147(f)(3) of USDA's Poultry Products Inspection Regulations. Section 170.60(b) (21 CFR 170.60(b)) also reflects FDA's belief that USDA had issued a prior sanction. This FDA regulation explicitly mentions a prior sanction covering the use of nitrates and/or nitrites "in the commercial curing of meat and meat products and poultry products * * *". Thus, although FDA had not issued a prior sanction for nitrates and nitrites in poultry products, the Commissioner believed that USDA, the agency with primary jurisdiction over meat and poultry products, had done so. On this basis, FDA included the prior sanctions in § 170.60 and proposed to include them in §§ 121.2007 and 121.2008.

Assistant Secretary Foreman's April 22, 1977 letter to the Commissioner squarely rebuts the assumption on which FDA had previously operated. The letter states that "[B]ased upon our review of available information, it does not appear that there is such a prior sanction or approval of nitrates and nitrites in poultry products." In the absence of prior sanctions, FDA must determine—as Assistant Secretary Foreman's letter requests—whether there is any other legal basis for the use of nitrates and nitrites in poultry products. Initial inquiry must be directed to the question of whether nitrates and nitrites in poultry products are "food additives" or "color additives", or both, as those terms are defined in section 201 (s) and (t) of the act. The answer depends on the purposes for which the substances are used.

Assistant Secretary Foreman's letter states: "nitrates and nitrites 'impart color' when added to white or brown poultry meat in that nitrates and nitrites cause such poultry meat to turn a reddish color." Nitrates and nitrites added to poultry products would appear, therefore, to meet the definition of a color additive in section 201(t) of the act. Indeed, if nitrates or nitrites are used solely for coloring, they are clearly color additives. However, FDA has not approved a color additive petition for nitrates or nitrites in poultry products under section 706 of the act (21 U.S.C. 376) and neither currently appears on the list of colors provisionally listed for use in food in § 81.1 (21 CFR 81.1)).

On the other hand, consideration of the levels of nitrates and nitrites currently permitted by USDA for use in poultry products suggests that the substances are being used, and have been permitted for use, for purposes in addition to imparting color. Indeed, it would appear that the predominant purposes for which nitrates and nitrites are used in poultry products are other than coloring. The amount of nitrates or nitrites needed to fix color in a poultry product is approximately 20 ppm. Yet USDA regulations under 9 CFR 381.147(f)(3) permit up to 200 ppm nitrates or nitrites in finished poultry products. That level is the amount generally thought necessary to prevent the growth of *Clostridium botulinum* and the formation of toxin, and thus to preserve products in which such formation might occur.

It is well established that when a tolerance is necessary for safe use, no food additive or color additive may be used in food in excess of the amount reasonably required to produce the intended effect; see sections 409(c)(4) and 706(b)(7) of the act (21 U.S.C. 348(c)(4), 376(b)(7)). Thus, although 9 CFR 381.147(f)(3) does not identify preservation or characterizing effects as the purposes for which nitrates and nitrites are used in poultry products, the amounts permitted by USDA suggest that these noncolor uses are, and generally have been, the predominant functions of nitrate and nitrite use.*

A substance used to preserve food is a food additive unless it falls within one of the exceptions to the statutory definition. The definition of a "food additive" in section 201(s) of the act excludes a number of categories of substances added to food—including substances that were sanctioned by USDA or FDA prior to September 6, 1958, substances generally recognized as safe (GRAS), and color additives. As previously noted, USDA has advised that it had not sanctioned the use of nitrates and nitrites in poultry products prior to the effective date of the Food Additives Amendment of 1958. The Commissioner concludes that nitrates and nitrites used in poultry products are neither prior-sanctioned nor covered by any other exception to the statutory definition of "food additive".

As previously explained, the definition of "food additive" in section 201(s) of the act excludes GRAS substances. While nitrates and nitrites in poultry products may at one time have been considered GRAS, they are not now viewed as GRAS by FDA, nor does the Commissioner have any indication that USDA now considers them to be GRAS.

As noted above, one effect of adding nitrates and nitrites to poultry products is to impart color. The statutory definition of color additive could be read literally to include any substance that imparts color, and the statutory definition of food additive to exclude any substance that is a color additive, thus making the two categories of substances mutually exclusive. The Commissioner does not believe that this result was intended by Congress, and it does not correspond with sound public policy or historical practice under the act. In the Color Additive Amendments of 1960, Congress was amending a statute under which, since 1958, substances used to color food had been treated as food additives or as coal tar dyes. A primary purpose of the Color Additive Amendments of 1960 was to do away with these differences in the treatment of color additives. As stated in the Report of the House Committee on Interstate and Foreign Commerce, accompanying H.R. 7624, the amendments: would do away with the differences in legal require-

ments and treatment as between the so-called coal-tar colors and other color additives, and would establish an integrated and internally consistent basis for determining the admissibility of any coloring material for use in or on foods, drugs, or cosmetics (other than hair dyes). This would be accomplished by excepting color additives (as defined in the bill) from the term "food additive"; repealing the present provisions for listing and certification of coal-tar colors; enacting, as part of a single section (sec. 706), comprehensive provisions for the separate listing of any color additives suitable and safe for general or restricted use in foods, drugs, or cosmetics, and for their certification (or exemption from certification) and making other amendments to the act to mesh with these provisions.

The bill would embrace all color additives whether or not synthesized and whether or not capable of derivation from a coal-tar constituent. From the point of view of determining safety of use, there is no sound scientific basis for distinguishing between a color additive extracted from a plant, animal, or mineral source and one which is synthesized with a chemical structure which will bring it under the term "coal-tar color". The bill would therefore establish common ground rules for all such colors.

There is no evidence in the legislative history of the Color Additive Amendments of 1960 that Congress, when it modified the definition of food additive, intended to exempt additives to foods that are used primarily for a purpose other than coloring but also satisfy the sweeping definition of color additive. Rather, the intent appears to have been to exempt those substances used solely as color additives from the definition of food additives so that petitioners for "non-coal-tar" colors would be relieved of the burden of having to demonstrate safety twice, under both the food additive and the color additive provisions of the act.

Section 70.3(g) of the FDA color additive regulations (21 CFR 70.3(g)) has been interpreted consistently with the recognition that a substance may be both a food additive and a color additive, reflecting the fact that some ingredients added to food may serve more than one technological purpose. Thus, the exception for color additives in section 201(s) does not preclude a substance from being both a color additive and a food additive, depending on its uses and effects, and therefore subject to the requirements of both sections 409 and 706 of the act.

Therefore, nitrates and nitrites, when used in poultry products at levels necessary to accomplish their preservative effect, are food additives within the meaning of section 201(s) of the act. No food additive petition for the use of nitrates and nitrites as a preservative in poultry products, however, has been approved by FDA. Furthermore, as previously noted, neither nitrates nor nitrites are currently approved as color additives or listed among the colors provisionally authorized for use in food.

It might be argued that, under these circumstances, a literal reading of the act requires immediate termination of the use of nitrates and nitrites in all poultry products. In the Commissioner's judgment, however, such precipitous action would fail to take into account the important health benefits that preservatives provide in preventing botulism, and therefore such action may not be warranted for the protection of the public health. Although significant safety issues have been raised about the use of nitrates and nitrites, their immediate elimination from all poultry and meat products would likewise pose serious safety concerns.

Some current uses of nitrates and nitrites may not be necessary to prevent the growth of *Clostridium botulinum*. There may also be uses in poultry that result in the formation of nitrosamines in foods before they are eaten. Consequently, the Commissioner believes that the immediate objective of both USDA and FDA should be to eliminate all nonpreservative uses of nitrates and nitrites for which substantial evidence of safety is lacking. This document is directed to this end and to establish a schedule for the completion of any further testing needed to resolve the questions of the safety of the addition of nitrates and nitrites to poultry products where nitrosamines are not performed, and to identify, and eliminate, any uses in poultry that result in preformed cancer-causing nitrosamines.

In the past, when the Commissioner has been reasonably certain that a substance with a long history of use may continue to be used safely, FDA has issued an interim food additive regulation that permits continued but limited use while required data are accumulated to enable the agency to make a final decision about the approvability of the substance (see 21 CFR Part 180).

The Commissioner has reached no final judgment about whether an interim food additive regulation covering even restricted uses of nitrates and nitrites in poultry products would be appropriate. However, he will consider proposing to establish an interim food additive regulation if USDA or other interested parties submit appropriate requests. The criteria for issuing an interim food additive regulation are set forth in § 180.1. Requests must address each criterion and provide all pertinent data and information needed to enable the agency to evaluate fully the request. The information required is more fully described in the concluding section of this notice.

The authority of FDA to issue interim food additive regulations permitting continued use of substances about which safety questions have been raised pending the accumulation of data to resolve those questions has been judicially upheld (*Jacobson* v. *Edwards*, Civil Action No. 445-71 (D.D.C. July 6, 1971), CCH FDC Reports paragraph 40, 817, p. 42, 114, *aff'd* No. 71-2046 (D.C. Cir. Dec. 15, 1972)).

Agency regulations make no provision for the issuance of "interim color additive regulations," however, and some question might be raised about FDA authority to add a substance to the provisional list of colors for the first time in 1977, some 17 years after the passage of the Color Additive Amendments of 1960. Although the Commissioner would have reservations about placing nitrates and nitrites on the provisional list at this late date, it is his opinion, upon careful consideration of the provisions and history of the 1960 amendments, that under appropriate circumstances, nitrates and nitrites could lawfully be so added. The legality of such action, however, is but one issue to be addressed. Clearly, the more important issue is whether nitrates and nitrites used as color additives are or would be safe. The Commissioner has no reason at the present time to propose the addition of nitrates and nitrites to the provisional list of colors. So far as he is now aware, neither type of substance is being used in poultry products solely for the purpose of affecting color. While some current users of nitrates and nitrites in poultry products undoubtedly desire the coloring effect of nitrates and nitrites used for preservation, FDA has not historically required dual approval of additives used for purposes that also affect color.

The Commissioner therefore will not require the submission of companion requests for both interim food additive status and provisional color listing for any use of nitrates or nitrites as a preservative or characterizing ingredient in poultry products.

The Commissioner would consider petitions for the "permanent" listing of nitrates or nitrites used solely for the purpose of coloring, at levels no higher than necessary to accomplish a coloring effect. If, contrary to his current understanding, nitrates and nitrites are currently being used in poultry products essentially as color additives, the Commissioner would also entertain requests for their provisional listing as color additives, subject to the following conditions: (1) A petition for "permanent" listing is filed simultaneously; (2) the requested color additive uses are ones that were in commercial use prior to July 12, 1960; (3) the Commissioner can be satisfied that provisional listing would pose no significant risk to public health; and (4) the request is accompanied by a commitment promptly to conduct the studies necessary to establish the safe conditions of use.

Issues on Which Data and Views Are Requested

The most important criterion for issuance of an interim food additive regulation under § 180.1 is the assurance that continued use of a substance will pose no significant risk to the health of consumers. In determining whether, for any uses in poultry products, nitrates and nitrites satisfy this criterion, the Commissioner will consider all information submitted with any requests for interim food additive status or for provisional color additive listing. He will also welcome views and scientific data submitted

by other interested persons and organizations, including the USDA Expert Panel that is considering the uses of nitrates and nitrites in curing meat and poultry products.

Before concluding that continued use of nitrates or nitrites in a product does not pose a significant risk to human health, the Commisioner must be satisfied that such use does not result in the formation of cancer-causing nitrosamines in the food before it is ingested, regardless of whether such formation occurs during production or when the product is prepared for eating. In addition, the Commissioner will carefully evaluate all available data relating to the toxicity of nitrates and nitrites when directly ingested.

To assist persons who wish to comment on, or submit data concerning, the policy announced in this document, the Commissioner has identified several questions on which the agency specifically requests information and advice:

(1) To what extent is botulinal toxin a genuine concern in poultry products? Which products?

(2) To what extent are nitrates and nitrites effective in preventing the growth of *C. botulinum* and formation of botulinal toxin in poultry products? Are there other compounds that would be equally effective? What levels of nitrates and nitrites are needed to prevent the growth of *C. botulinum* and formation of botulinal toxin?

(3) What is the chemical action of nitrates/nitrites in poultry products?

(4) What is the biochemical mechanism of the coloring or color-fixing properties of nitrates and nitrites?

(5) What additional studies are necessary to resolve the foregoing questions, as well as the outstanding safety issues discussed above?

The Commissioner advises that he will entertain requests for the issuance of interim food additive regulations or for provisional listing as a color additive. To the extent that the types of data identified in questions (1) through (4) above cannot be presented in response to this notice, requestors must express a willingness to commit themselves to conduct any studies that are necessary for resolution of the unanswered questions within a reasonable period of time. This requirement would obviously extend to any studies identified in the comments received in response to question (5).

A request for an interim food additive regulation is not required to be accompanied by a request for provisional listing and a petition for "permanent" listing as a color additive to support a coloring effect that is a consequence of the food additive use for which the request is filed. The Commissioner concludes that any request providing sufficient supporting grounds for the proposal of an interim food additive regulation would at the same time be sufficient to support the safety of any coloring effect. Therefore, the Commissioner does not, at this time, perceive any useful purpose to be served by requiring an accompanying color additive petition in these circumstances. If the Commissioner should conclude that additional information is needed with respect to any coloring effect, he would require further submissions in the future.

Dated: August 25, 1977.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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